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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/054,387 | 01/22/2002 | Minzhen Xu | REH-2011 | 8989 |

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| EXAMINER | |
|---|---|
| FREDMAN, JEFFREY NORMAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/054,387 | XU ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *97-155* is/are pending in the application.

4a) Of the above claim(s) *101-155* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *97-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 97-104, and of the species SEQ ID NO: 40 in the replies filed December 19, 2003 and May 7, 2004, is acknowledged. Claims 105-155 drawn to the nonelected groups and claims 101-104 drawn to non-elected species are withdrawn.

### *Priority*

2. The current application is not given benefit of priority to parent applications 09/036,746 and 08/661,627 because neither of these applications provides descriptive support for the current claims. Specifically, claim 97 requires that SEQ ID NO: 1, CTCGGTACCTACTGG, be excluded. However, SEQ ID NO: 1 is not even present in either of the two cited parent applications. As MPEP 2163 notes "to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure." Since the sequence limitation is not supported by the disclosure of parent applications 09/036,746 and 08/661,627, this application is currently given a priority of December 4, 1998, the filing date of 09/205,995.

### *Claim Interpretation*

3. Prior to analysis of claim 97 over the prior art, the claim must be interpreted in light of the prior art. Claim 97 specifically excludes the antisense oligomer sequence 5' CTCGGTACCTACTGG 3' (SEQ ID NO: 1). This same sequence is listed in the Sequence listing as SEQ ID NO: 1. The Sequence rules, specifically 37 CFR

1.822(c)(5), note "A nucleotide sequence shall be presented, only by a single strand, in the 5 to 3 direction, from left to right." Therefore, SEQ ID NO: 1 is not the same oligonucleotide as that used in the Bertolino et al (International Immunol. (1991) 3(5):435-443) reference at figure 2, which is 5' GGTCATCCATGGCTC 3', but rather is the reverse sequence from that disclosed by Bertolino. While it is not indefinite what sequence is excluded, given that a particular sequence is described, it is unclear if Applicant's intent was to exclude the sequence of Bertolino. Given that ambiguity, two rejections will be made under the prior art. The 102 rejection will address the generic claims 97-100 as written. The 103 rejection will address both the specific nucleotide sequence elected and the issue of selection of other oligonucleotides.

4. Applicant is specifically referred to MPEP 2161-2163 for treatment of "new matter" prior to amendment of the sequence.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 97-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Bertolino et al (International Immunol. (1991) 3(5):435-443).

Bertolino teaches a method for displaying an autodeterminant peptide (see abstract), in association with a MHC class II protein, on the surface of a

MHC class II-positive antigen presenting cell (see abstract and page 436, column 2), comprising;

a) providing the MHC class II-positive antigen presenting cell which does not contain an exogenous construct encoding mammalian B7 molecule (see page 436, column 2, where mouse fibroblastic cells were transfected with several different vecotrs, none of which are identified by Bertolino as B7); and

b) introducing into the MHC class II-positive antigen presenting cell, a specific regulator of Ii protein expression or immunoregulatory function, the oligonucleotide CTCGGTACCTACTGG (SEQ ID NO: 1) being specifically excluded, the specific regulator consisting essentially of a copolymer of from 10 to 50 nucleotide bases, the copolymer being characterized by the ability to hybridize specifically to a target region of the RNA molecule encoding mammalian Ii protein under physiological conditions, wherein the specific regulator is characterized by the ability to inhibit Ii expression (see page 436, column 2, subheading "Antisense oligodeoxynucleotide experiments", and page 437, figure 2, where Bertolino teaches the use 5' GGTCATCCATGGCTC 3' for antisense inhibition, which is different than SEQ ID NO: 1 that is excluded, is between 10 and 50 nucleotide bases and is shownto inhibit Ii proteins in figure 3 under physiological conditions).

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 97-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bertolino et al (International Immunol. (1991) 3(5):435-443) in view of Koch et al (EMBO J. (1987) 6: 1677-1583) and further in view of either of Bennett et al (U.S. Patent 5,514,788), Anderson et al (U.S. Patent 5,442,049) and Cowsert et al (U.S. Patent 5,945,290)

Bertolino teaches a method for displaying an autodeterminant peptide (see abstract), in association with a MHC class II protein, on the surface of a MHC class II-positive antigen presenting cell (see abstract and page 436, column 2), comprising;

a) providing the MHC class II-positive antigen presenting cell which does not contain an exogenous construct encoding mammalian B7 molecule (see page 436, column 2, where mouse fibroblastic cells were transfected with several different vecotrs, none of which are identified by Bertolino as B7); and

b) introducing into the MHC class II-positive antigen presenting cell, a specific regulator of Ii protein expression or immunoregulatory function, the oligonucleotide CTCGGTACCTACTGG (SEQ ID NO: 1) being specifically excluded, the specific regulator consisting essentially of a copolymer of from 10 to 50 nucleotide bases, the copolymer being characterized by the ability to hybridize specifically to a target region of the RNA molecule encoding mammalian Ii protein under physiological conditions, wherein the specific regulator is characterized by the abilïty to inhibit Ii expression (see page 436, column 2, subheading "Antisense oligodeoxynucleotide experiments", and page 437, figure 2, where Bertolino teaches the use 5' GGTCATCCATGGCTC 3' for antisense inhibition, which is different than SEQ ID NO: 1 that is excluded, is between 10 and 50 nucleotide bases and is shownto inhibit Ii proteins in figure 3 under physiological conditions).

Bertolino does not teach the complete nucleic acid sequence which encodes the Ii protein, though Bertolino cites Koch for that sequence (see 442, column 2) and provides an exon/intron map in figure 2.

Koch teaches the specific sequence which encodes the Ii protein, including a sequence with 100% homology to SEQ ID NO: 40 (see attached alignment).

With regard to the specific exclusion of SEQ ID NO: 1 as well as the use of other oligonucleotides such as SEQ ID NO: 40 that are selected from the nucleic acid sequence encoding the Ii protein, each of Bennett, Anderson and Cowsert teach that selection of antisense oligonucleotides is routine in the prior art and that targets of antisense oligonucleotides include the translation initiation site (see Bennett, column 5,

line 59 to column 6, line 20; See Anderson, column 5, lines 24-39; See Cowsert, column 5, lines 1-30). Cowsert further notes and teaches how to select antisense targets (see column 3) and directs antisense formation to the translation initiation site (see column 3, lines 22-35, noting "a preferred intragenic site is the region encompassing the translation initiation or termination codon of the open reading frame of the gene.").

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to select alternate sequences for inhibition of the Ii expression as taught by Bertolino from the sequence of Koch (cited by Bertolino for the sequence) since Bennett teaches,

> "Antisense oligonucleotides hold great promise as therapeutic agents for the treatment of many human diseases. Oligonucleotides specifically bind to the complementary sequence of either pre-mRNA or mature mRNA, as defined by Watson-Crick base pairing, inhibiting the flow of genetic information from DNA to protein. The properties of antisense oligonucleotides which make them specific for their target sequence also make them extraordinarily versatile. Because antisense oligonucleotides are long chains of four monomeric units they may be readily synthesized for any target RNA sequence. Numerous recent studies have documented the utility of antisense oligonucleotides as biochemical tools for studying target proteins. Rothenberg et al., J. Natl. Cancer Inst. 1989, 81, 1539-1544; Zon, G. Pharmaceutical Res. 1988, 5, 539-549). Because of recent advances in synthesis of nuclease resistant oligonucleotides, which exhibit enhanced cell uptake, it is now possible to consider the use of antisense oligonucleotides as a novel form of therapeutics. (3) Antisense oligonucleotides offer an ideal solution to the problems encountered in prior art approaches. They can be designed to selectively inhibit a given isoenzyme, they inhibit the production of the enzyme, and they avoid non-specific mechanisms such as free radical scavenging or binding to multiple receptors. A complete understanding of enzyme mechanisms or receptor-ligand

> interactions is not needed to design specific inhibitors. (see column 5, line 59 to column 6, line 20)."

So Bennett provides significant motivation to the ordinary artisan to design antisense oligonucleotides as a biochemical tool to study target proteins such as the Ii protein of Bertolino, especially where Bertolino specifically teaches the use of an antisense oligonucleotide to study the Ii protein.

Further motivation to direct the ordinary artisan to design antisense oligonucleotides specifically to the translation initiation site is provided by Cowsert, who notes "a preferred intragenic site is the region encompassing the translation initiation or termination codon of the open reading frame of the gene. (column 3, lines 22-35)". So Cowsert provides motivation to limit the preferred target selection site to a very small region of translation initiation area of the gene, limiting the number of possible targets in the Ii sequence to an extremely small genus size.

All three of Anderson, Cowsert and Bennett teach the presence of a reasonable expectation of success, with Anderson showing a table of 22 different antisense oligonucleotides at Table 4, all of which had significantly greater antisense activity than the negative control. Of course, the only oligonucleotide tested by Bertolino functioned.

With regard to the selection of the specific oligonucleotide of SEQ ID NO: 40, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed antisense oligonucleotides simply represent structural homologs of the antisense oligonucleotide of Bertolino, which are derived from sequences taught by Koch and suggested by the prior art of Bertolino as useful for antisense oligonucleotides, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed antisense oligonucleotide of SEQ ID NO: 40 is *prima facie* obvious over the cited references in the absence of secondary considerations. This is particularly the case given the suggestion of the specific region from which SEQ ID NO: 40 was derived by both Bertolino and Cowsert, who limit the number of possible species to a relatively small genus.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637

6/21/04